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Using a Developmental Perspective to Examine the Moderating Effects of Marriage on Heavy Episodic Drinking in a Young Adult Sample Enriched for Risk

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Abstract

Epidemiological data consistently demonstrate that being married (relative to being single or separated/divorced/widowed) is associated with lower alcohol use and lower odds of alcohol use disorder (Bachman, O'Malley, & Johnston, 1984; Grant et al., 2015; Leonard & Rothbard, 1999). The protective effects of marriage are often explained in terms of role incompatibility (Yamaguchi & Kandel, 1985) and social control processes (Craddock, vanDellen, Novak, & Ranby, 2015), whereby individuals match their behaviors with the socially normative expectations of the spousal role (Horn, Xu, Beam, Turkheimer, & Emery, 2013; Kendler, Lönn, Salvatore, Sundquist, & Sundquist, 2016), and spouses monitor and control one another's health behaviors, such as drinking (Craddock, vanDellen, Novak, & Ranby, 2015; Umberson, 1992). Above and beyond these main effects, marital status moderates genetic influences on alcohol use behaviors

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such that genetic risk is typically attenuated among married compared to unmarried individuals (Barr et al., 2017; Heath, Jardine, & Martin, 1989; Kendler et al., 2016; Prescott & Kendler, 2001). Such findings are consistent with the idea that genetic influences are attenuated in environments in which there is a high degree of social control (Shanahan & Hofer, 2005).

Although the protective and moderating effects of marriage on alcohol use are among the most consistent findings in the epidemiological (Leonard & Eiden, 2007) and genetic epidemiological literatures (Barr et al., 2017; Heath et al., 1989; Kendler et al., 2016; Prescott & Kendler, 2001), the majority of these studies have examined these effects at a single point in time, typically in midlife adults or in age-mixed samples (e.g., Dinescu et al., 2016; Heath et al., 1989; Horn et al., 2013; Kendler et al., 2016). This has left a gap in our understanding of these associations and gene-environment interaction processes from a developmental perspective. In particular, marriage may not have a protective effect when it occurs developmentally off-time, such as among those who marry relatively early. Although there is no standard definition of what constitutes early marriage, researchers often use a cut-point below the national median, with some using 23 (Uecker & Stokes, 2008) and others using 25 years of age (Eickmeyer & Hemez, 2017). Early marriage is associated with negative consequences in the areas of educational attainment, finances, and health (Dupre & Meadows, 2007; Elder; 1994; Lehrer, 2004; Uecker, 2014). Many of these consequences are long-lasting and continue to negatively impact individuals, specifically women, throughout adulthood (Loughran & Zissimopoulous, 2004; Uecker, 2012). Early marriage is also associated with more role confusion and conflict (Elder, 1994), lower relationship stability, and poorer relationship quality (Lehrer, 2004). In short, the negative outcomes associated with early marriage contrasts with the protective effect typically associated with marriage observed in older samples.

It is important to recognize that some of the poor outcomes associated with early marriage may also reflect selection effects (Miller, 2014). Individuals who marry young also tend to be less educated, have fewer aspirations to obtain more education (Eickmeyer & Hemez, 2017; Uecker & Stokes, 2008), and have less-educated parents who also married young (Uecker & Stokes, 2008). There is also some evidence that individuals who marry at younger ages engage in more substance use as adolescents (Leonard & Rothbard, 1999) and are more likely to have a history of psychiatric illness (Forthofer, Kessler, Story, & Gotlib, 1996). Thus, individuals who marry relatively early (and their partners) may have a number of personal liabilities that limit the protective effects of marriage (Grant et al., 2007).

A second limitation of prior studies on marriage and alcohol outcomes is that they have typically focused on population- or community-based samples (e.g., Bachman et al., 1984; Horn et al., 2013; Kendler et al., 2016; Leonard & Rothbard, 1999). Risk and protective factors for alcohol outcomes in population-based samples may differ from those in high-risk individuals, such as among individuals with family histories of alcohol use disorder (Hill, Shen, Lowers, & Locke, 2000). A family history of alcohol use disorder is associated with greater risk for problematic alcohol use and the development of alcohol problems (Cotton, 1979; Kendler et al., 2015). Of particular relevance for this study is that a parental history of alcohol problems is associated with a greater likelihood of having a spouse with an alcohol

use disorder (Salvatore et al., 2018). Considering that marriage to a spouse with an alcohol problem is a risk factor for the onset of alcohol problems (Kendler et al., 2016; Leonard & Eiden, 2007), high-risk individuals may be placed at even greater risk given their decreased likelihood of entering into the types of marital relationships with prosocial partners that are likely to have a protective effect on alcohol misuse.

Current Study

To address these gaps in the literature, we report findings from a longitudinal study of a sample of young adults enriched for risk who were followed between ages 21 and 25 where we examined (1) whether marriage was associated with frequency of heavy episodic drinking, and (2) whether marital status moderated measured genetic influences (as measured with a genome-wide polygenic risk score) to predict frequency of heavy episodic drinking across time. Genome-wide polygenic risk scores reflect a state-of-the-science approach to index one's level of genetic predisposition for a given trait or behavior (Wray et al., 2014). This approach uses the results from a genome-wide association study (GWAS) in a large-scale discovery sample to calculate personalized indices of genetic risk in a target sample. Common genetic variants, or single nucleotide polymorphisms (SNPs), are tested for their association with a given trait/behavior in the discovery sample (Bogdan, Baranger, & Agrawal, 2018; Maier, Visscher, Robinson, & Wray, 2018; Salvatore et al., 2014; Wray et al., 2014). Then, the effect sizes from the discovery GWAS are used to calculate the weighted linear composite corresponding to the number of risk-increasing alleles carried by each individual in the target sample.

If marriage has a consistent protective effect across development, we would expect that marriage would be associated with reductions in heavy episodic drinking (Bachman et al., 1984; Grant et al., 2015; Leonard & Rothbard, 1999). Similarly, if marriage has a uniformly moderating protective effect on genetic risk across development, we would expect that genetic risk would be attenuated for those who are married compared to those who are unmarried (Barr et al., 2017; Heath, Jardine, & Martin, 1989; Kendler et al., 2016; Prescott & Kendler, 2001). However, given that early marriage is associated with poorer outcomes across a range of domains (e.g., educational attainment, finances, and health; Dupre & Meadows, 2007; Elder; 1994; Lehrer, 2004; Uecker, 2014), we did not advance directional hypotheses for either research question.

Method

Participants

We used data from the Prospective Study sample of the Collaborative Study on the Genetics of Alcoholism (COGA). COGA is a collaborative research project between multiple sites in the US, with the goal of identifying genetic influences on alcohol use disorders and related psychiatric outcomes (Begleiter et al., 1995). Families with alcohol dependent probands, based on both the Diagnostic and Statistical Manual of Mental Disorders, third edition, revised (DSM-III-R; American Psychiatric Association, 1987) and Feighner criteria (Feighner et al., 1972), were recruited from inpatient and outpatient alcohol clinics across six study sites in the US and followed longitudinally. Unascertained comparison families

from the population were also recruited from various sources (e.g., driver's license records and dental clinics). The Institutional Review Boards of all participating institutions approved the study, and written consents were obtained from all participants. Detailed description about the design of COGA can be found in previously published papers (Begleiter et al., 1995; Foroud et al., 2000; Reich et al., 1998).

The Prospective Study was launched in 2004 as a part of COGA, with the goal of examining how genetic risk unfolds across development and in conjunction with the environment. Offspring between ages 12 and 22 with at least one parent in either the clinically ascertained group or the unascertained comparison group who had completed an interview in the original COGA study were recruited to participate and followed longitudinally (Bucholz et al., 2017). In this study, we included 937 (776 from the clinically ascertained group) European ancestry participants (based on ancestral principal components derived from genetic data) between the ages of 21 and 25 with available genetic data. We limited our sample to only participants of European ancestry so that our analytic sample was ancestrally matched to the discovery sample used to calculate genome-wide polygenic scores. Participants were followed-up biennially, with each participant assessed up to three times between ages 21 and 25, resulting in a total of 1,691 assessments. In total, 34.8%, 50.0%, and 15.3% of participants completed one, two, and three assessments.

Measures

Heavy episodic drinking frequency

Frequency of heavy episodic drinking (HED) was measured at each assessment by asking, "How often did you have five or more drinks in 24 hours during the last 12 months?" Responses included 13 options ranging from "never" to "every day," which were converted into frequencies by taking the midpoint of each response option. For example, the responses "every day" and "two days per week (100–149 days)" corresponded to 365 and 124.5 days per year, respectively. Those who reported they did not drink during the past year were coded as zero.

Marital status

Marital status was measured at each assessment. Six response options were combined to create a binary variable for each time point. "Married" and "living as married" were combined and coded as married (1). All other response options (i.e., "widowed," "separated," "divorced," and "never married") were combined and coded as unmarried (0). (We note that there were no widowed participants in the sample.) This approach is consistent with previous studies of the moderating effect of relationship status on genetic risk for alcohol phenotypes (e.g., Heath et al., 1989). Individuals whose marital status changed (e.g., from married to divorced) were coded differently across time.

Genotyping

Genotyping was performed using the Illumina 1M and Illumina OmniExpress (Illumina, San Diego, CA), and Smokescreen (BioRelm, Walnut, CA) arrays. The reported pedigree structure was assessed using a pruned set of 1,519,440 SNPs. Family structures were

altered, as needed, and SNP genotypes were tested for Mendelian inconsistencies (Pedcheck; O'Connell & Weeks, 1998) with the revised family structure. Genotype inconsistencies were set to missing. Genotypes were imputed to 1000 Genomes (EUR and AFR, Phase 3, b37, October 2014; build hg19) using SHAPEIT (Delaneau, Zagury, & Marchini, 2013) and then IMPUTE2 (Howie, Fuchsberger, Stephens, Marchini, & Abecasis, 2012). Imputed SNPs with information (INFO) scores < 0.30 or individual genotype probability scores < 0.90 were excluded, as were palindromic SNPs (A/T or C/G), monomorphic SNPs, SNPs with a genotyping rate of < 95%, SNPs that did not pass Hardy-Weinberg equilibrium (HWE; $p < 1 \times 10^{-6}$), and SNPs with a minor allele frequency (MAF) < 0.05%. In total, 6,881,872 SNPs were available for analysis after passing quality control and data cleaning thresholds.

Genome-wide polygenic risk scores (PRS) of alcohol use in the COGA sample were constructed based on GWAS summary statistics of alcohol consumption, measured in grams of alcohol per day, from the Alcohol Genome-Wide Association (AlcGen) and Cohorts for Heart and Aging Research in Genomic Epidemiology Plus (CHARGE+) consortia (Schumann et al., 2016). After removing palindromic SNPs (which can be ambiguous with respect to the reference allele when going across samples), we used the *clump* and *score* procedures in PLINK (Purcell et al., 2007) to sum each individual's total number of minor alleles from the score SNPs, with each SNP weighted by the negative log of the GWAS association *p*-value and sign of the association coefficient (beta). Clumping was done with respect to the linkage disequilibrium (LD) pattern in the 1000 Genome Phase 3 sample using a 500kb physical distance and an LD threshold of $r^2 >= 0.25$. Thus, PRS were constructed of SNPs that capture independent genetic association signals from the AlcGen and CHARGE+ GWAS. Following conventions for polygenic scoring using the pruning and thresholding approach (Bogdan et al., 2018), we calculated a series of scores in COGA that included SNPs meeting increasingly stringent *p*-value thresholds in the AlcGen and CHARGE+ discovery GWAS (Schumann et al., 2016; $p < 0.50$, $p < 0.40$, $p < 0.30$, $p < 0.20$, $p < 0.10$, $p < 0.05$, $p < 0.01$, $p < 0.001$, and $p < 0.0001$).

Data Analysis

To examine whether marital status moderated the association between the PRS and HED among young adults and whether the association between marital status (treated as a time-varying variable), PRS, and HED changed across time, we used a generalized linear mixed model (GLMM) with log link by assuming the HED follows a Poisson distribution. In this model, HED frequency was predicted by age, marital status, PRS, two-way interactions, and the three-way interaction between age, PRS, and marital status. Age was centered at 21 years. Sex was coded as female (0) or male (1) and included as a covariate. The first three ancestral principal components were also included as covariates to control for potential population stratification. Random effects of intercept and age were included to incorporate repeated assessments.

Following standard practice (Bogdan et al., 2018; Purcell et al., 2009), we first conducted a series of preliminary analyses to select the PRS *p*-value threshold that provided the best fit and maximized effect sizes. In these models, the log of HED frequency was regressed onto age, PRS, marital status, the two-way interactions, and the three-way interaction between

age, PRS, and marital status. The selected PRS was standardized and used in all subsequent analyses. We then fit GLMMs with marital status and the selected PRS separately to examine the main effects of the predictors on HED. In each model, marital status or PRS and its interaction with age were included as predictors for HED. We then fit and interpreted the full model with marital status, the selected PRS, the two-way interactions, and the three-way interaction between age, PRS, and marital status. We used the GLIMMIX procedure in SAS and maximum likelihood estimator based on Laplace approximation for parameter estimation.

To check the robustness of the results, we ran two series of sensitivity analyses. First, we fit the same model with parental history of alcohol dependence (PHAD), in place of the PRS, to represent latent genetic risk for alcohol use problems (Kendler et al., 2015). A PHAD variable was created from parents' alcohol dependence (AD) diagnosis based on the fourth edition of the DSM (DSM-IV; American Psychiatric Association, 1994) criteria. PHAD was coded dichotomously as no parental history of AD (0) and either mother or father was diagnosed with AD (1). Participants were coded as missing if both parents' information was missing or if one parent did not have an alcohol disorder diagnosis and the other parent's information was missing. This resulted in 743 participants included in the sensitivity analyses. Parameters of PHAD and its interactions with marital status and age were compared with those from the original model.

Next, we conducted a secondary series of analyses to examine whether our pattern of results was robust when controlling for divorce/separation, college attendance, gene-by-covariate and covariate-by-environment interactions, and family ascertainment status. First, the original model was fit after removing participants who reported divorce or separation ($n = 36$) from the sample. This allowed us to rule out the possibility that our observed effects were due to the inclusion of divorced/separated individuals in the unmarried group in view of evidence that divorce and separation are associated with greater alcohol problems (Grant et al., 2015; Kessler, Walters, & Forthofer, 1998). Second, we fit a variation of the original model including college attendance as a time-varying covariate. College students engage in more heavy episodic drinking compared to their non-student age-matched peers (Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2015; O'Malley & Johnston, 2002; Slutske, 2005), so controlling for college attendance allowed us to examine whether our observed effects were driven by college attendance. Third, to address concerns that gene-by-environment effects may be confounded by the effects of gene-by-covariate and covariate-by-environment interactions (Keller, 2014), we fit a model including these interaction terms. Finally, to control for potential differences between the clinically ascertained and unascertained comparison families, we fit a variation of the original model including family ascertainment status as a time-invariant covariate.

Results

Descriptive statistics of marital status and HED frequencies by age are summarized in Table 1. More participants were married or living as married at older ages compared to at younger ages. Among unmarried participants of all ages, the majority were never married rather

than separated or divorced. On a descriptive level, engagement in HED was generally lower among married (or living as married) participants compared to those who were unmarried.

Table 2 summarizes fit statistics (AIC and BIC) and effect sizes for the preliminary analyses to inform selection of the PRS *p*-value threshold. The lowest values of both AIC and BIC were observed for the polygenic score based on *p*-value threshold of < .0001, indicating that the best model fit was obtained with PRS based on that threshold. Similarly, the absolute values of *t* for parameter estimates related to PRS were the largest with PRS based on $p < .0001$, indicating that the predictive power of PRS with that threshold was highest. Thus, a PRS based on a $p < .0001$ threshold was carried forward into subsequent analyses.

Before fitting a full model with all interactions between PRS and marital status, we fit separate models with either PRS or marital status to examine the main effects of each variable (see Table 3). The results from both models indicated that neither PRS nor marital status was predictive of HED frequencies, and none of the associations changed as a function of age. The only significant association was between HED and age, indicating that HED frequency decreased between ages 21 and 25.

Parameter estimates from the full model that included PRS, marital status, the two-way interactions, and the three-way interaction between PRS, marital status, and age are summarized in Table 4. We found a significant negative three-way interaction between PRS, marital status, and age, and we focus on the interpretation of this three-way interaction effect in view of the fact that this higher-order interaction modifies the main effects and lower-order interactions. Figure 1 depicts the pattern of the three-way interaction between PRS, marital status, and age, plotted at three illustrative ages (21, 23, and 25). Each plot shows the expected frequencies of HED by combinations of marital status and PRS, which was split at the median.

With age centered at 21, HED was similar among unmarried participants with high and low PRS. As illustrated in Figure 1, unmarried individuals with higher PRS were predicted to engage in HED 8.97 days per year compared to 11.59 days per year for those with lower PRS. However, among married participants, HED was higher among those with higher PRS compared with those with lower PRS. Married individuals with higher PRS were predicted to engage in HED 34.85 days per year compared with 4.72 days per year for those with lower PRS.

This pattern of effects changed over time, indicated by the negative three-way interaction. Centered at the illustrative age of 23, HED was similar across all conditions. Unmarried individuals with lower PRS were predicted to engage in HED 8.06 days per year compared to 6.96 days per year for those with higher PRS. Married individuals with lower PRS were predicted to engage in HED 5.99 days per year compared to 7.05 days per year for those with higher PRS. With age centered at 25, HED was similar among unmarried participants with high and low PRS. Unmarried individuals with higher PRS were predicted to engage in HED 5.72 days per year compared to 5.02 days per year for those with lower PRS. Among married participants, however, higher PRS was associated with lower HED. Individuals with higher PRS were predicted to engage in HED 1.86 days per year compared with 11.14 days

per year for those with lower PRS. Thus, the nature of marriage's moderating effect on the association between PRS and HED changed between ages 21 and 25.

Sensitivity analyses with parameters estimated from the same GLMM model fit with PHAD in place of PRS are summarized in Table 5 and depicted in Figure 2. At 21, consistent with the results from the model with the PRS, we found a significant positive interaction between PHAD and marital status, indicating that PHAD was associated with higher HED among married participants. Although the three-way interaction between age, PHAD, and marital status was not statistically significant, the direction of the negative three-way interaction was consistent with the result from the model using the PRS, indicating that the initial difference of the association between PHAD and HED by marital status was attenuated with age.

In a secondary set of sensitivity analyses, we examined whether our pattern of results was robust to the effects of divorce and separation, college attendance, gene-by-covariate and covariate-by-environment interactions, and family ascertainment status. We observed the same pattern of results after removing individuals who reported divorce or separation from the sample and when controlling for college attendance. Likewise, we observed the same pattern of results after controlling for all gene-by-covariate and covariate-by-environment interactions. Lastly, we observed the same pattern of results when controlling for family ascertainment status. None of our effects significantly changed with the inclusion of these covariates or interaction terms, which guided our decision to report the results with the fewest parameters in this paper (full results available upon request from the first author).

Discussion

The primary goals of the present study were to examine, in a sample of young adults enriched for risk, whether (1) marriage was associated with heavy episodic drinking, and (2) marital status moderated measured genetic influences to predict heavy episodic drinking across time.

We first examined the relationship between marital status and heavy episodic drinking, and we found no association. Our null effect is surprising, as previous research demonstrated a protective effect of marriage on alcohol use (Bachman et al., 1984; Grant et al., 2015; Leonard & Rothbard, 1999). These contradictory results could be due to discrepancies in sample characteristics, as previous research typically focused on midlife or age-mixed (e.g., Dinescu et al., 2016; Heath et al., 1989; Horn et al., 2013; Kendler et al., 2016), population- or community-based samples (e.g., Bachman et al., 1984; Horn et al., 2013; Kendler et al., 2016; Leonard & Rothbard, 1999). In contrast, the present study included a sample of young adults enriched for risk.

A sample of young adults enriched for risk, such as ours, may differ in important ways from previously studied samples for two reasons. First, the protective effect of marriage is typically explained by role incompatibility (Yamaguchi & Kandel, 1985; Horn et al., 2013; Kendler et al., 2016), which may not be relevant for young adults. Young adults may not perceive a conflict between high levels of alcohol use and the socially normative expectations of the spousal role; therefore, there may be less impetus to reduce alcohol

use upon the transition to marriage. Second, the null effect of marriage may be attributable to selection effects of a sample enriched for risk. Previous research demonstrates that individuals with a predisposition for alcohol problems are more likely to have a spouse with an alcohol use disorder (Salvatore et al., 2018), which may actually put individuals at greater risk for problematic alcohol use (Kendler et al., 2016; Leonard & Eiden, 2007). This suggests that individuals who are at higher risk for problematic alcohol use, like many of those in the present sample, are at increased risk of choosing partners with higher levels of alcohol use. Thus, the absence of a protective marriage effect in our sample may reflect that marriage to a partner with problematic alcohol use undermines the protective effect of marriage (Kendler et al., 2016).

Next, to test whether marital status was a relevant moderator of genetic influences on alcohol use across time, we examined the interaction between marital status, polygenic risk score, and age to predict heavy episodic drinking. Among married individuals at age 21, we found that heavy episodic drinking was higher among those with higher polygenic scores compared to those with lower polygenic scores. This finding is indicative of a pathogenic gene-by-environment interaction effect among those who marry early (i.e., by age 21), suggesting that early marriage does not have the same protective benefit in terms of attenuating genetic predispositions as seen in older samples (Dinescu et al., 2016; Heath et al., 1989; Horn et al., 2013; Kendler et al., 2016).

Interestingly, we found that the pathogenic gene-by-environment interaction effect decayed over time. Heavy episodic drinking was similar across all conditions by age 23, and by age 25, the effect was reversed. At age 25, we found that married individuals with higher polygenic scores had lower heavy episodic drinking compared to those with lower polygenic scores. In contrast, at age 25 heavy episodic drinking was similar among all unmarried participants, regardless of genetic risk. Our finding adds developmental nuance to the extant literature on gene-by-environment interaction effects for alcohol outcomes, in that it further suggests that marriage is not a uniformly protective environment. Moreover, it underscores the importance of examining intersecting risk and protective factors, with particular consideration of the potential ramifications of developmentally off-time events (e.g., being at greater genetic risk and marrying young).

Although polygenic scores reflect the state of the science when considering measured genetic risk for complex behavioral outcomes like alcohol use (Bogdan et al., 2018; Salvatore et al., 2014), we also recognize that, at present, they account for just a fraction of the variation. In order to examine whether our observed polygenic gene-by-environment effects were spurious, we ran two sets of sensitivity analyses. First, we ran a parallel set of analyses using parental history of alcohol dependence as our index of one's genetic predisposition. Consistent with our polygenic analyses, we found that, among married individuals at age 21, a parental history of alcohol dependence was associated with higher heavy episodic drinking compared to those without this parental history. However, the pattern of effects at age 25 differed across the polygenic risk score and parental history analyses. Specifically, there were no differences in heavy episodic drinking among married individuals as a function of parental history of alcohol dependence, but there were differences as a function of polygenic risk scores. Thus, although the polygenic risk

and parental history models are consistent in demonstrating that the pathogenic gene-by-environment effect decays over time, the inconsistent results across the polygenic risk and parental history models at age 25 caution against any strong conclusions about the exact nature of this decay (and whether the effect observed at age 21 fully reverses).

Second, we ran a set of set of analyses to examine whether our pattern of results was robust when controlling for divorce and separation status, college attendance, gene-by-covariate and covariate-by-environment interactions, and family ascertainment status. Prior research suggests that divorce and separation are associated with greater alcohol problems (Grant et al., 2015; Kessler et al., 1998) and that college students are more likely to engage in heavy episodic drinking than their non-college peers (Johnston et al., 2015; O'Malley & Johnston, 2002; Slutske, 2005). We observed the same pattern of effects after removing divorced and separated individuals from the unmarried group as was observed in the primary polygenic risk score analyses, allowing us to rule out the possibility that our observed effects were due to the inclusion of this subgroup. Likewise, we observed the same pattern of effects when controlling for college attendance, suggesting that our findings were not driven by individuals' college student status. Next, we reran our analyses controlling for gene-by-covariate and covariate-by-environment interactions to address any concerns that our gene-by-environment effects were confounded (Keller, 2014). When controlling for these interaction terms, we found a pattern of results that was consistent with those observed in the primary polygenic risk score analyses. Finally, after controlling for family ascertainment status, we observed the same pattern of effects as in our primary polygenic risk score analyses. This suggests that group-level differences between the clinically ascertained and unascertained community comparison families did not influence our results.

It is worth noting the differences in the association between polygenic risk and heavy episodic drinking across the main effect and interactive effect models. In the main effects model, we found no association between polygenic risk and heavy episodic drinking. However, in the interaction model where we examined marriage as a moderator of the association between polygenic risk and heavy episodic drinking, a statically significant main effect of polygenic risk emerged. Importantly, main effects cannot be directly interpreted in the presence of an interaction effect (Aiken & West, 1991). Moreover, the null effect of the polygenic risk score in the main effects model, and its moderation by marital status in the interaction model, underscores that genetic influences on complex traits, such as heavy episodic drinking, can have a differential impact depending on the environment. Consistent with this possibility, in this study we observed a crossover effect for the polygenic risk score as a function of participants' marital status and age. This suggests that the association between polygenic risk and heavy episodic drinking is dependent on marital status, such that genetic liability had a stronger impact on heavy episodic drinking among individuals who married relatively young.

Implications

In the present study, we show that marriage is not uniformly protective among a sample of young adults enriched for risk. Our findings suggest that although early marriage itself was not a risky environment, this environment seemed to exacerbate risk for those

with higher polygenic load. These results add an interesting developmental perspective on some of the earliest gene-by-environment effects in the field and highlight the importance of utilizing a gene-by-environment-by-development approach (Vrieze, Iacono, & McGue, 2012). Moreover, it emphasizes the need to examine intersecting risk and protective factors within this framework. These findings can aid future clinical work aimed at reducing heavy episodic drinking by informing risk profiling. As our findings suggest that early marriage exacerbates the effects of genetic risk for alcohol misuse, individuals who marry young and who are genetically predisposed to alcohol problems may be an especially important group to target to reduce heavy drinking.

Limitations

The findings from our study should be considered in the context of several limitations. First, the present study included offspring of either clinically ascertained families or unascertained comparison families. Thus, the offspring of the unascertained comparison families may not necessarily have the same risk factors as offspring from the clinically ascertained families (although we note that comparison families were not excluded on the basis of a history of substance use disorders). Second, because the COGA Prospective Study employs a rolling enrollment strategy and we limited our sample to participants between 21–25 years of age, some participants were only eligible for one assessment while still in our specified age range. Of note, the model that we employed can incorporate different numbers of assessments and periods between assessments across participants so that we were able to maximize the sample size from the available data. Third, we did not have any data on the characteristics of our participants' partners, which would likely influence the drinking frequency of the participants, nor did we have information regarding the relationship length (particularly for those who were living as married), to consider the potential moderating effects of these factors.

Lastly, there was an imperfect correspondence between our sample and the discovery sample used to create polygenic scores. The discovery sample consisted of older individuals from a population-based sample (Schumann et al., 2016), while the target sample in the present study consisted of a group of young adults enriched for risk. Moreover, our study only included participants of European ancestry; therefore, it is possible that our findings may not extend to individuals of other ancestral backgrounds. Future research should address these limitations by utilizing a better matched and more ethnically diverse discovery sample, although we note that most large-scale GWAS efforts for complex traits and behaviors such as alcohol are limited in this respect at this time given the massive sample sizes required to detect small effects. Additionally, our study incorporated individuals from a sample enriched for risk, so it is unclear if our findings would generalize to other populations.

Conclusions and Future Directions

Previous studies of marital status as a moderator of genetic risk for alcohol outcomes have typically utilized cross-sectional studies, without considering the role of development. We examined whether marriage was a relevant moderator of genetic risk on alcohol use using a developmental framework in a sample of young adults enriched for risk. We observed

pathogenic gene-by-environment effects among married individuals at age 21, but these effects decayed over time. Additionally, this work can be expanded to more critically examine the pathogenic effect of early marriage on genetic risk for alcohol use. Finally, future research should examine whether these findings extend to developmentally off-time marriages in the opposite direction (i.e., individuals whose first marriage occurs much later in life), particularly in view of findings that individuals who are at-risk for alcohol problems (by virtue of family history) or have alcohol problems themselves tend to marry later (Salvatore et al., 2018; Waldron et al., 2011). Overall, our findings highlight the importance of utilizing a gene-by-environment-by-development approach and considering the consequences of developmentally off-time events.

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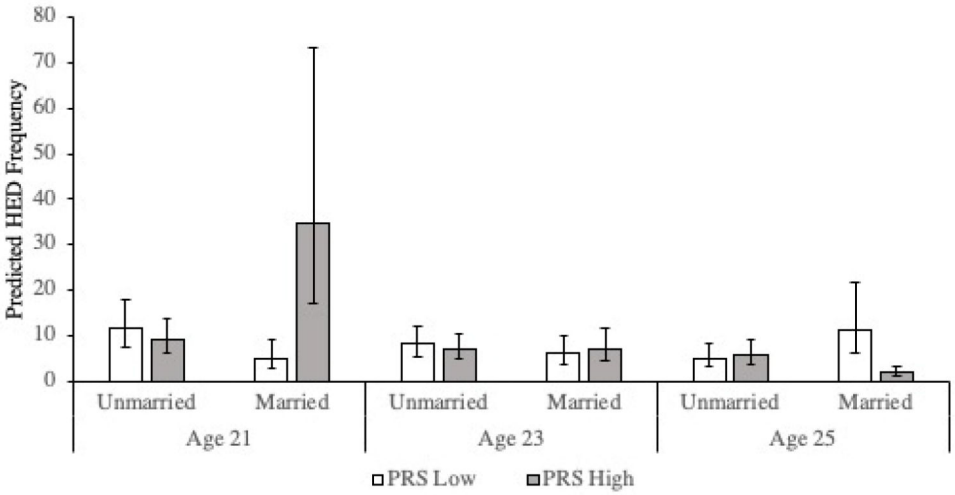

Figure 1:

Heavy episodic drinking as a function of the three-way interaction of *Alc-PRS,* marital status, and time. *Notes.* CIs are not symmetric because they were converted from expected log-transformed counts. The first three ancestral principal components and sex were included as covariates. HED frequency was measured in days over the last 12 months. Abbreviations: CI = Confidence interval; HED = Heavy episodic drinking; PRS = Genome-wide polygenic risk score for alcohol.

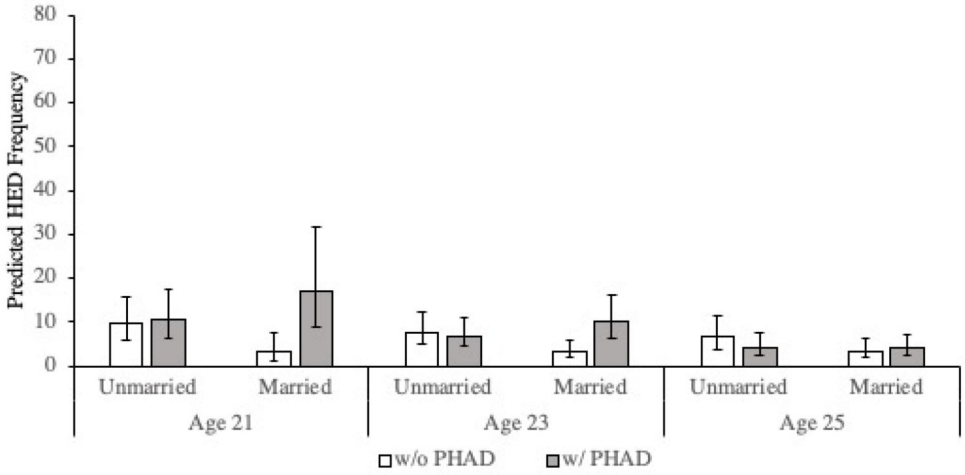

Figure 2.

Heavy episodic drinking as a function of the three-way interaction between parental history of alcohol disorder, marital status, and time. *Notes.* CIs are not symmetric because they were converted from expected log-transformed counts. The first three ancestral principal components and sex were included as covariates. HED frequency was measured in days over the last 12 months. Abbreviations: CI = Confidence interval; HED = Heavy episodic drinking; PHAD = Parental history of alcohol disorder.

Table 1.

Marital status and heavy episodic drinking frequencies by age.

		Married		Unmarried			Mean (SD) HED Frequency	
Age	***N***	**% Married**	**% Living as Married**	**% Never Married**	**% Separated**	**% Divorced**	**Unmarried**	**Married**
21	422	7.8	5.2	86.5	0.20	0.20	47.8 (63.5)	21.8 (48.5)
22	368	11.1	7.9	79.1	0.80	1.10	48.0 (69.0)	19.5 (40.4)
23	356	14.0	10.7	73.3	0.80	1.10	46.4 (65.2)	19.0 (41.4)
24	301	24.3	10.3	62.5	1.00	2.00	42.5 (64.5)	21.6 (52.4)
25	244	23.0	10.3	62.3	2.10	2.50	35.7 (52.1)	21.8 (52.8)

Married includes those living as married. HED frequency was measured in days over the last 12 months. Abbreviations. HED = Heavy episodic drinking.

Table 2

Parameter estimates and fit statistics for *Alc-PRS* thresholds.

Parameter	Fit Statistics		*T*-Values			
***P*-Value Threshold**	**AIC**	**BIC**	***Alc-PRS***	**Age* *Alc-PRS***	***Alc-PRS**Marital Status**	**Age* *Alc-PRS**Marital Status**
<.0001	15474.06	15546.97	2.07	1.87	5.53	8.52
<.001	15557.73	15630.64	1.16	0.56	4.73	3.62
<.01	15582.58	15655.49	0.40	0.18	0.47	0.34
<.05	15574.68	15647.59	0.21	0.96	1.11	1.30
<.1	15577.32	15650.23	0.07	0.76	0.93	0.86
<.2	15578.8	15651.71	0.10	0.53	0.53	0.21
<.3	15581.42	15654.33	0.07	0.28	0.29	0.27
<.4	15581.66	15654.57	0.10	0.30	0.26	0.31
<.5	15578.31	15651.22	0.11	0.55	0.40	0.26

T-values shown are the absolute values. Analogous to the full model, age was centered at 21 years and heavy episodic drinking frequency was log-transformed. The first three ancestral principal components and sex were included as covariates. Abbreviations. *Alc-PRS* = Genome-wide polygenic risk score for alcohol.

Table 3.

Heavy episodic drinking as a function of marital status and *Alc-PRS* and their interaction with time.

	Marital Status Only			***Alc-PRS* Only**		
Parameter	**b**	**SE**	**95% CI**	**b**	**SE**	**95% CI**
Intercept	***1.65***	***0.29***	***[1.08, 2.22]***	***1.64***	***0.29***	***[1.07, 2.21]***
Sex (Female = 0)	***1.21***	***0.16***	***[0.89, 1.54]***	***1.21***	***0.16***	***[0.89, 1.53]***
PC1	20.03	45.07	[−69.07, 109.13]	19.94	45.06	[−69.14, 109.02]
PC2	1.14	19.81	[−38.02, 40.30]	−20.46	19.78	[−59.57, 18.64]
PC3	−4.09	11.31	[−26.46, 18.27]	−21.77	11.34	[−44.19, 0.64]
Time (Age − 21)	***−0.16***	***0.04***	***[−0.23, −0.09]***	***−0.18***	***0.04***	***[−0.25, −0.11]***
Marital Status	0.23	0.20	[−0.17, 0.63]	-	-	-
Time*Marital Status	−0.10	0.06	[−0.22, 0.01]	-	-	-
Alc-PRS	-	-	-	−0.04	0.10	[−0.23, 0.15]
Time**Alc-PRS*	-	-	-	−0.03	0.03	[−0.10, 0.04]

Bold type indicates $p < .05$. ***Bold italic*** type indicates $p < .001$. Abbreviations. PC = Principal component for genetic ancestry; *Alc-PRS* = Genome-wide polygenic risk score for alcohol.

Table 4.

Heavy episodic drinking as a function of *Alc-PRS*, marital status, time, and their interaction.

Parameter	b	SE	95% CI
Intercept	***1.64***	***0.29***	***[1.06, 2.22]***
Sex (Female = 0)	***1.21***	***0.16***	***[0.89, 1.54]***
PC1	22.29	45.47	[−67.60, 112.18]
PC2	0.52	20.01	[−39.04, 40.07]
PC3	−4.42	11.42	[−26.99, 18.16]
Time (Age − 21)	***−0.15***	***0.04***	***[−0.22, −0.07]***
Alc-PRS	**−0.21**	**0.10**	**[−0.41, −0.01]**
Marital Status	0.28	0.21	[−0.13, 0.70]
Time**Alc-PRS*	0.07	0.04	[0.00, 0.14]
Time*Marital Status	**−0.14**	**0.06**	**[−0.26, −0.02]**
*Alc-PRS**Marital Status	***1.21***	***0.22***	***[0.77, 1.64]***
Time**Alc-PRS**Marital Status	***−0.56***	***0.07***	***[−0.68, −0.43]***

Bold type indicates $p < .05$. ***Bold italic*** type indicates $p < .001$. Abbreviations. PC = Principal component for genetic ancestry; *Alc-PRS* = Genome-wide polygenic risk score for alcohol.

Table 5.

Sensitivity analyses of heavy episodic drinking as a function of parental history of alcohol disorder, marital status, time, and their interaction.

Parameter	b	SE	95% CI
Intercept	***1.52***	***0.36***	***[0.82, 2.22]***
Sex (Female = 0)	***1.23***	***0.19***	***[0.86, 1.61]***
PC1	13.69	51.27	[−87.96, 115.33]
PC2	−6.49	23.48	[−53.04, 40.07]
PC3	−1.05	12.99	[−26.80, 24.71]
Time (Age − 21)	−0.10	0.06	[−0.22, 0.01]
PHAD	0.08	0.23	[−0.37, 0.53]
Marital Status	−0.84	0.43	[−1.68, 0.01]
Time* PHAD	−0.11	0.08	[−0.26, 0.05]
Time*Marital Status	0.08	0.12	[−0.16, 0.31]
PHAD *Marital Status	**1.65**	**0.50**	**[0.65, 2.64]**
Time* PHAD *Marital Status	−0.24	0.14	[−0.52, 0.03]
Observations		743	

Bold type indicates $p < .05$. ***Bold italic*** type indicates $p < .001$. Abbreviations. PC = Principal component for genetic ancestry; PHAD = Parental history of alcohol disorder.